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(Article begins on next page)

Biallelic mutations in the ciliary gene *TMEM67* cause RHYNS syndrome

Running Title: Recessive *TMEM67* mutations cause RHYNS syndrome

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Conflict of interests

The authors declare that they have no conflict of interests

40 **ABSTRACT**

41 A rare syndrome was first described in 1997 in a 17-year-old male patient presenting
42 with *Retinitis pigmentosa*, *HYpopituitarism*, *Nephronophthisis* and *Skeletal dysplasia*
43 (RHYNS). In the single reported familial case, two brothers were affected, arguing for
44 X-linked or recessive mode of inheritance. Up to now, the underlying genetic basis of
45 RHYNS syndrome still remains unknown. Here we applied whole-exome sequencing in
46 the originally described family with RHYNS to identify compound heterozygous
47 mutations in the ciliary gene *TMEM67*. Sanger sequencing confirmed a paternally
48 inherited nonsense (p.Arg208*) and a maternally inherited missense mutation
49 (p.Asp430Gly). Overall, *TMEM67* showed one of the widest clinical continuums
50 observed in ciliopathies ranging from early lethality to adults with liver fibrosis.
51 Our findings extended the spectrum of phenotypes/syndromes resulting from biallelic
52 *TMEM67* mutations to now eight distinguishable clinical conditions including RHYNS
53 syndrome.

54

55 *Key words:* ciliopathy; nephronophthisis; retinitis pigmentosa; *MKS3*; *TMEM67*

56

57 INTRODUCTION

58 RHYNS syndrome (OMIM 602152) was defined in 1997 by the acronym of Retinitis
59 pigmentosa, HYpopituitarism, Nephronophthisis and mild Skeletal dysplasia in a 17-
60 year-old man¹. A closely resembling phenotype with liver fibrosis has been previously
61 described in a boy², while Hedera and collaborators reported a similar condition in a
62 family with two affected brothers³. The observation of affected males only and
63 recurrence in a sib suggested either an X-linked or autosomal recessive inheritance
64 pattern. Yet, the underlying genetic basis has remained unexplained, although the
65 pattern of associated clinical features was compatible with a hereditary ciliary disorder.
66 In this study, we reported the 20-year follow-up of the original patient with RHYNS
67 syndrome. Whole-exome sequencing led to the identification of a compound
68 heterozygous mutation in the gene *TMEM67*. The assignment of RYHNS syndrome as
69 part of the wide spectrum of *TMEM67*-related ciliopathies is discussed.

70

71 SUBJECTS AND METHODS

72 Patient

73 The index male patient was re-evaluated at the age of 38 years, still in search of a
74 molecular diagnosis after receiving a clinical diagnosis of RHYNS syndrome at young
75 age¹. In brief, he was born with congenital palsy of the III and IV cranial nerve on the
76 right resulting in complete ophthalmoplegia and upper eyelid ptosis and congenital
77 palsy of the VI cranial nerve on the left with exotropia. At the age of 4 years, he
78 measured 90 cm (-4,9SD) and showed delayed bone age. Growth hormone (GH) and
79 thyreotropin releasing hormone (TSH) deficiency were diagnosed and treated with
80 replacement therapy until young adulthood. At this age, radiological examination

81 showed mild signs of skeletal dysplasia consisting of osteopenia, thin tubular bones,
82 epiphyseal hypoplasia and hypoplastic iliac bones with irregular acetabular margins. At
83 age 11, retinitis pigmentosa and left sensorineural hearing loss were first diagnosed.
84 Abnormal renal function was evident by age 12 years, when a renal biopsy
85 demonstrated a histological pattern consistent with nephronophthisis. Due to the
86 worsening of renal function he underwent a first kidney transplantation from a deceased
87 donor at age 29; but it was rejected. Subsequently, he was started on hemodialysis and,
88 at age 34, a second renal transplantation from deceased donor was performed. Since
89 then, his clinical condition remained stable.

90 We have evaluated the patient at age 38 years, when he measured 152 cm of height with
91 weight 63,5 kg. Generalized and severe osteoporosis was diagnosed by DEXA
92 examination (femoral head: T-Score -3.5, Z-Score -3.0, BMD 0,458 g/cm²; lumbar
93 region: T-Score -3.1, Z-Score -3.0, BMD 0,752 g/cm²). A novel skeletal survey detected
94 moderately shortened long bones, bowed radii, short femoral neck, brachydactyly at
95 hands and feet with more severe involvement of middle phalanges, distal phalanx of the
96 thumbs and metacarpals, moderately thickened calvarium, rotoscoliosis of mild degree,
97 and a posterior arch defect of the sacrum. Diffuse reduction of the bone density with
98 thinning of the diaphyseal cortex, was evident, particularly on hands (Figure 1).

99 Hormonal dosage showed increased parathyroid hormone (PTH) levels in the blood
100 (164 pg/ml, reference range 14-72 pg/ml), despite having received kidney
101 transplantation. Beside this, all other hormonal levels (including thyroid, pituitary and
102 steroid hormones) were repeatedly checked to be within the normal range. Of note, liver
103 enzymes were repeatedly tested normal as was dedicated liver ultrasound.

104 Audiometry showed pantonal left-sided moderate-to-severe sensorineural hearing loss.
105 Ophthalmologic examination confirmed no residual visual acuity and complete
106 extinguishment of the electroretinogram in both eyes.

107 Neuropsychological evaluation excluded functional deficits while brain imaging was
108 normal. He obtained the chartered accountant qualification and he was completely self-
109 sufficient in all daily life activities, although he did not have an employment.

110

111 **Whole-Exome Sequencing**

112 In order to determine the genetic etiology of the RHYNS syndrome, WES was
113 performed hypothesizing an underlying autosomal recessive inheritance pattern. Exome
114 capture and next-generation sequencing was carried out at Otogenetics Ltd.

115 (<http://www.otogenetics.com>) on an Illumina HiSeq2000 (Illumina, San Diego, CA)
116 platform and indexed libraries were subjected to paired-end (2×100 bp read length)
117 sequencing-by-synthesis using fluorescent reversible terminators. Exome enrichment
118 was conducted following the protocol for the SeqCap EZ Human Exome beads (Roche
119 NimbleGen, Inc., Madison, WI, USA). Three µg DNAs, isolated from peripheral blood
120 of the affected patient, his parents and two unaffected brothers were submitted for WES.
121 Sequence reads were mapped to the human reference genome assembly (GRCh37/hg19)
122 using CLC Genomics Workbench™ software (CLC bio, Aarhus, Denmark). Variants
123 were called, filtered, and prioritized according to their pathogenicity scores obtained
124 from the MutationTaster, CADD, and Polyphen-2 web interfaces. Furthermore, variants
125 were cross-referenced with the Human Gene Mutation Database (HGMD,
126 <http://data.mch.mcgill.ca/phexdb>), and genes known to be implicated in ciliopathy-
127 related disorders were prioritized.

128

129 **RESULTS**

130 Two mutations in *TMEM67* (NM_153704.5; MIM*609884) were identified in the
131 proband, each inherited from a heterozygous parent, consistent with compound
132 heterozygosity and autosomal recessive inheritance. The two identified mutations were
133 confirmed by Sanger sequencing, namely, a nonsense mutation (c.622A>T, p.Arg208*)
134 in exon 6 (paternal allele), and a missense mutation (c.1289A>G, p.Asp430Gly) near
135 the splice acceptor site of exon 13 (maternal allele). The two healthy brothers were
136 carriers of the nonsense mutation only (Figure 2). The missense variant was absent from
137 the 1000 Genomes Project, the Exome Aggregation Consortium (ExAC,
138 <http://exac.broadinstitute.org>) and the Genome Aggregation Database (gnomAD,
139 <http://gnomad.broadinstitute.org>); conversely, the nonsense mutation was present at
140 extremely low frequency in population databases (17 and 49 heterozygous individuals
141 in ExAc and gnomAD, respectively). The nucleotide and deduced protein change were
142 predicted as “disease causing” by the *in silico* pathogenicity prediction program
143 MutationTaster (<http://mutationtaster.org>) which also predicted for the c.1289A>G a
144 potential alteration of the acceptor splice site. In particular, using the Human Splicing
145 Finder software (<http://www.umd.be/HSF3/index.html>) this mutation was predicted to
146 abolish the canonical acceptor site with formation of a novel site leading to a shorter (-4
147 bases) exon 13. The software also predicted the formation of an exonic splicing silencer
148 and the alteration of exonic splicing enhancer.

149

150 **DISCUSSION**

151 In this study, we report the identification of biallelic mutations in the *TMEM67* gene as

the underlying genetic defect causative of RHYNS syndrome. These findings extend the spectrum of phenotypes resulting from *TMEM67* mutations to now eight distinguishable ciliopathies (Table 1). Their clinical manifestations display a wide range of presentations ranging from lethal phenotypes to patients with organ-specific involvement. Mutations in this gene were initially identified in Meckel syndrome, a lethal disorder displaying central nervous system (CNS) malformations, typically occipital encephalocele, multicystic kidneys, ductal plate dysplasia with congenital hepatic fibrosis (CHF) and postaxial polydactyly⁴. Subsequently, Baala and collaborators identified *TMEM67* mutations in three patients with *pure* (isolated) Joubert syndrome (JS), thus defining the sixth JS locus (JBTS6)⁵. Indeed, different subtypes of JS were associated to *TMEM67* mutations with distinct genotype-phenotype correlations within the spectrum of JS-related disorders (JSRDs), a group of pleiotropic ciliopathies which share in common the Molar Tooth Sign (MTS) at brain imaging⁶. In particular, the strongest correlation was defined with JS and CHF, since around 70% patients affected by so-called COACH syndrome (Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, ocular Coloboma, and Hepatic fibrosis) carried biallelic *TMEM67* mutations⁷.

In addition to Meckel syndrome and JSRDs, about 10% of patients affected by nephronophthisis (NPHP) and CHF without neurological involvement and normal brain imaging (NPHP11; MIM #613550) had *TMEM67* mutations⁸. Interestingly, the same gene was also mutated in three children with a unique association of polycystic kidney (mimicking autosomal recessive polycystic kidney disease - ARPKD), NPHP, CHF and midbrain-hindbrain abnormalities within the MTS spectrum⁹. More recently, Tarailo-Graovac et al.¹⁰ described a young adult patient with two mutations in *TMEM67*, who

176 displayed, in addition to the MTS and cerebellar atrophy at brain imaging, mild
177 intellectual disability, adolescent-onset dementia, vertical gaze palsy, ataxia, and
178 progressive hepatic fibrosis, overlapping Niemann-Pick type C manifestations. Lastly,
179 *TMEM67* was mutated in an otherwise healthy adult patient affected by isolated
180 congenital hepatic fibrosis, which represented so far, the mildest end of the *TMEM67*-
181 related spectrum¹¹.

182 This intriguing clinical heterogeneity associated with mutations in one and the same
183 gene calls for the delineation of specific genotype-phenotype correlations. The allelic
184 spectrum of *TMEM67* includes missense, truncating and splice site mutations, as well as
185 rare multiexon deletions. Two truncating mutations (either frameshift, nonsense or
186 splice site mutations) occur with high frequency in Meckel syndrome and are not
187 reported in non-lethal phenotypes¹². Conversely, two missense mutations or a
188 combination of truncating /splicing and missense mutations are prevalent in less severe
189 phenotypes within the JSRD spectrum, i.e. JS and COACH⁷. Hypomorphic mutations in
190 *TMEM67* are associated with NPHP and liver fibrosis (NPHP11), while more than half
191 of these patients display ocular involvement⁸. Interestingly, our patient carried one
192 truncating and one splicing mutation and his phenotype was mainly characterized by
193 retinitis pigmentosa, NPH without any neurologic involvement or liver fibrosis. The
194 absence of either neurologic or hepatic involvement is surprising since these are major
195 manifestations of *TMEM67* mutations (Table 1). Altogether these observations
196 emphasize the role of, yet unidentified, modifier factors in other genes modulating the
197 penetrance of clinical manifestations. Of note, mutations at different loci interacting
198 epistatically under a “multiallelic” inheritance has been proposed as a model for disease
199 penetrance in ciliopathies such as Bardet-Biedl syndrome and nephronophthisis^{13,14}.

200 In addition, our patient had hypopituitarism without structural abnormalities of the
201 pituitary gland on brain MRI. Interestingly, growth hormone deficiency was not
202 considered a major feature of JS, but recently two distinct genes (*KIAA0753* and
203 *CELSR2*) were associated with such endocrine anomalies in ciliopathies, strengthening
204 the importance of ciliary function also in the development of the pituitary gland^{15,16}.
205 In conclusion, our data place RHYNS syndrome within the spectrum of *TMEM67*-
206 related ciliopathies. This is one of the widest clinical continuums resulting from
207 recessive mutations in a single gene, ranging from early lethality to adults with liver
208 fibrosis. More studies are encouraged to decipher modifier factors influencing the
209 penetrance of clinical manifestations in ciliopathies.

210 **List of abbreviations:**

- 211 ARPKD: Autosomal Recessive Polycystic Kidney Disease
- 212 CHF: congenital hepatic fibrosis
- 213 CNS: central nervous system
- 214 COACH: Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, ocular
- 215 Coloboma, and Hepatic fibrosis
- 216 EDTA: ethylenediaminetetraacetic acid
- 217 ExAC: Exome Aggregation Consortium
- 218 GH: growth hormone
- 219 gnomAD: Genome Aggregation Database
- 220 HGMD: Human Gene Mutation Database
- 221 JS: Joubert syndrome
- 222 JSRDs: Joubert syndrome related disorders
- 223 MTS: molar tooth sign
- 224 NPHP: nephronophthisis
- 225 PTH: parathyroid hormone
- 226 RHYNS: Retinitis pigmentosa, HYpopituitarism, Nephronophthisis and Skeletal
- 227 dysplasia.
- 228 TSH: thyreotropin releasing hormone
- 229 WES: whole exome sequencing

230 **APPENDIX:**

231 List of the members of the “Undiagnosed Disease Network Italy”: Domenica Taruscio
232 (Rome, Italy); Marco Salvatore (Rome, Italy); Maria Chiara De Stefano (Rome, Italy);
233 Federica Censi (Rome, Italy); Giovanna Floridia (Rome, Italy); Francesco Brancati
234 (L'Aquila, Italy); Giuseppe Novelli (Rome, Italy); Erica Daina (Ranica, Italy);
235 Paraskevas Iatropoulos (Ranica, Italy); Alessandra Ferlini (Ferrara, Italy); Marcella Neri
236 (Ferrara, Italy); Dario Roccatello (Turin, Italy); Simone Baldovino (Turin, Italy); Elisa
237 Menegatti (Turin, Italy); Bruno Bembi (Udine, Italy)

238

239 **Declarations:**

240 Availability of data and materials

241 All data generated or analyzed during this study are included in this published article.

242 Authors' contributions

243 FB and EO had full access to all of the data in the study and take responsibility for the
244 integrity of the data and the accuracy of the data analysis. FB, EO and NP were
245 responsible for the study supervision. LC drafted the manuscript and interpreted the
246 data. EC collected clinical data. VVW performed sequencing analysis. LC, EC and
247 VVW equally contributed to the manuscript. AC is in charge of the patient and
248 contributed relevant clinical data for phenotypic delineation. MC reviewed the skeletal
249 X-Ray images and contributed relevant clinical data for phenotypic delineation. A
250 critical revision of the manuscript for important intellectual content was carried out by
251 FS, GN and NP. UDNI contributed to the administrative, technical and material support.
252 All authors contributed to the study concept and design. All authors were responsible
253 for drafting of the manuscript, contributed to the acquisition, analysis and interpretation

254 of data, read and approved the final manuscript.

255 Consent for publication

256 The participants included in the study signed a written informed consent to publish their
257 data.

258 Ethics approval and consent to participate

259 The research protocol, in accordance with the tenets of the Declaration of Helsinki and
260 their reviews, was approved by the Ethics Committee. The patients included in the study
261 signed a written informed consent to participate in the study.

262 Acknowledgements

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317 **Titles and legends to figures**

318

319 Figure 1: Radiological skeletal survey of the proband at age 38 years.

320 (a) Thickened calvarium. (b) Short and bowed radius. (c) Brachydactyly at hands with
321 more severe involvement of middle phalanges, distal phalanx of the thumbs and
322 metacarpals. Generalized reduction of bone density with thinning of the diaphyseal
323 cortex is observed. (d) Rotoscoliosis. (e) Posterior arch defect of the sacrum and short
324 femoral necks.

325

326 Figure 2: Pedigree of the RHYNS family and *TMEM67* electropherograms.

327 (a) Family tree showing the proband (filled square symbol) and two healthy sibs.
328 Circles and squares indicate females and males, respectively. (b) Genomic sequence
329 electropherograms demonstrate a nonsense mutation (c.622A>T, p.Arg208*) in the
330 father (I-1) and all 3 sons (II-1, II-2, II-3) and a missense mutation (c.1289A>G,
331 p.Asp430Gly) in the affected son (II-1) and his mother (I-2). Arrows indicate a
332 compound heterozygous mutation in the affected son and heterozygous changes in all
333 other individuals.

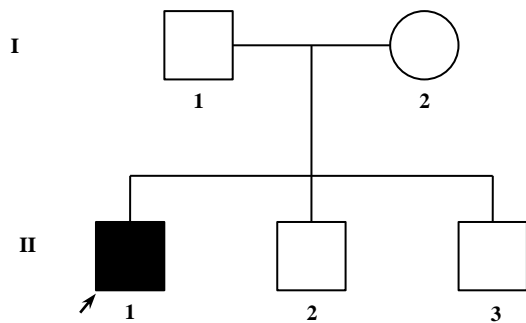
334

335 **Legend to table:**

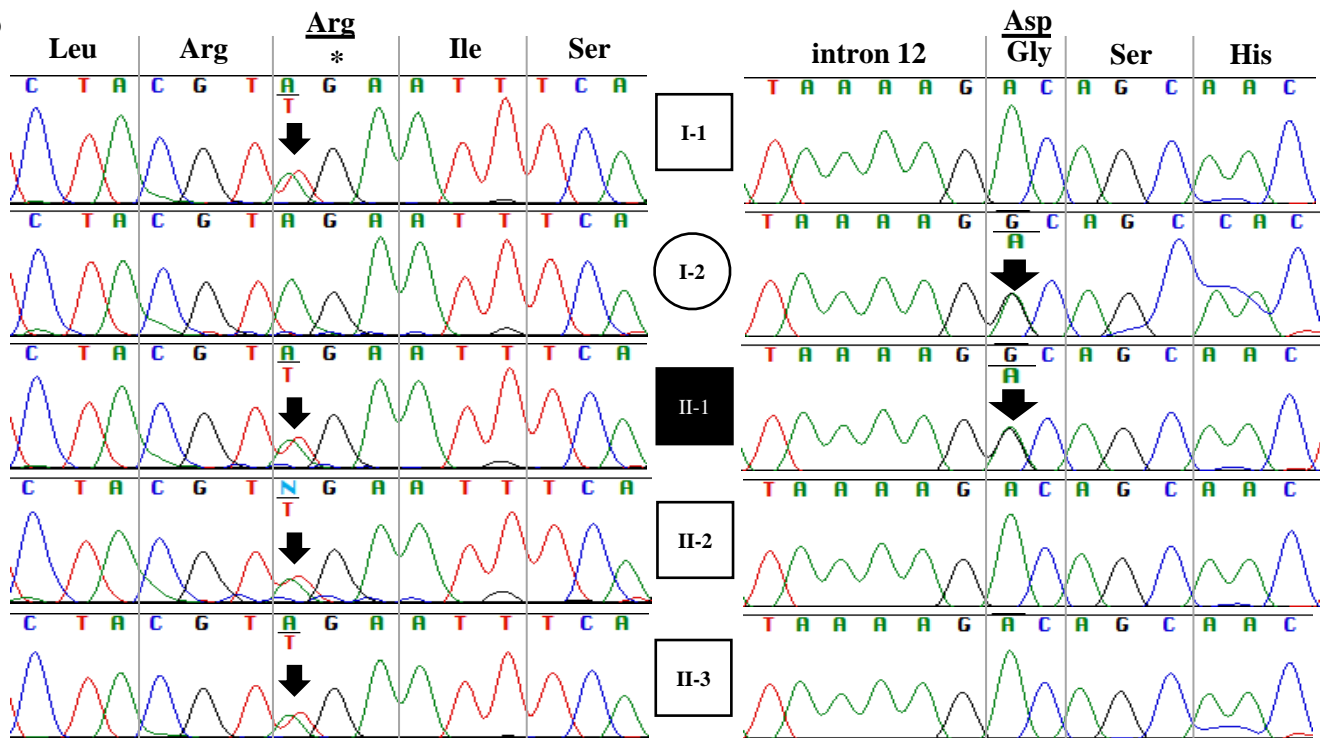
336 Table 1: *TMEM67*-related phenotypes and distinctive clinical manifestations.



a



b



TMEM67 exon 6
 c.622A>T, p.Arg208*

TMEM67 exon 13
 c.1289A>G, p.Asp430Gly

Table 1. *TMEM67*-related phenotypes and distinctive clinical manifestations.

Syndrome	Major clinical features	Number of reported patients	Representative references
Meckel syndrome	<ul style="list-style-type: none"> • Occipital encephalocele • Cystic dysplastic kidneys • Ductal plate malformation • Hepatic fibrosis • Postaxial polydactyly 	49	Smith et al. ⁴ Khaddour et al. ¹⁷
Joubert syndrome	<ul style="list-style-type: none"> • Molar tooth sign • Intellectual disability (variable) • Hypotonia • Irregular breathing pattern • Eye movement abnormalities 	30	Baala et al. ⁵ Vilboux et al. ⁶
COACH	<ul style="list-style-type: none"> • Molar tooth sign • Intellectual disability (variable) • Ataxia • Ocular coloboma • Hepatic fibrosis • Medullary cystic renal disease • Nephronophthisis 	31	Brancati et al. ⁷ Doherty et al. ¹⁸
NPHP11	<ul style="list-style-type: none"> • Nephronophthisis • Hepatic fibrosis 	8	Otto et al. ⁸ Srivastavaa et al. ¹⁹
ARPKD-like	<ul style="list-style-type: none"> • Molar tooth sign-like • Speech apraxia • Polycystic kidneys • Nephronophthisis • Hepatic fibrosis 	3	Gunay-Aygun et al. ⁹
Niemann-Pick C phenocopy	<ul style="list-style-type: none"> • Molar tooth sign • Cerebellar atrophy at young age • Intellectual disability • Gaze palsy • Ataxia • Adolescent-onset dementia • Hepatic fibrosis 	1	Tarailo-Graovac et al. ¹⁰
Isolated congenital liver fibrosis	<ul style="list-style-type: none"> • Hepatic fibrosis in an otherwise healthy adult man 	1	Vogel et al. ¹¹
RHYNS	<ul style="list-style-type: none"> • Retinitis pigmentosa • Gaze palsy • GH- and TSH-deficiency • Nephronophthisis • Skeletal dysplasia • Sensorineural hearing loss 	1	This report

Table legend: ARPKD: Autosomal Recessive Polycystic Kidney Disease; COACH: Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, ocular Coloboma, and Hepatic fibrosis; GH: growth hormone; NPHP: Nephronophthisis; RHYNS: Retinitis pigmentosa, HYpopituitarism, Nephronophthisis and Skeletal dysplasia; TSH: thyreotropin releasing hormone